REMARKS/ARGUMENTS

The Remarks are being filed in response to the Office Action mailed on May 2, 2007. Claims 1-15 are pending. Claims 3 and 11 have been canceled. No new matter has been added.

Claim Rejections - 35 U.S.C. § 112, first paragraph

The Examiner rejected claims 1-15 as failing to comply with the enablement requirement. Namely, the Examiner states that the breadth of the claims are too broad and that the working examples are insufficient to enable one of skill in the art to practice the invention.

The Applicant respectfully disagrees for the following reasons. Table 1 provides detailed results of a study performed on a dog, which the Examiner acknowledges as showing a statistically significant change in the cholesterol and trigylcerides as measured for the dog. The Examiner disputes whether Table 2 provides statistical significance in a human study, however, and on this basis states that the claims are not enabled to practice the invention on humans. First, the Applicant respectfully submits that "[c]ompliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed. An example may be 'working' or 'prophetic.' A working example is based on work actually performed. A prophetic example describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually achieved." MPEP § 2164.02. Moreover, "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors. To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." Id.

The Applicant respectfully submits that one of skill in the art would readily be able to extrapolate the data from the disclosure, including Table 1, to practice the present claims. It is well-established in various scientific fields that the results of animal studies, particularly those of mammals, can be applied to humans. In fact, among mammals, most of the host defense mechanisms (barrier and immune) and metabolic (anabolic and catabolic) systems are similar. See e.g., Biologic Markers in Urinary Toxicology (1995). Looking at the pharmaceutical

companies, most if not all of the studies conducted are first performed on laboratory animals. Those results from the pre-clinical studies are then used to obtain preliminary efficacy and pharmacokinetic information to extrapolate the test compound to human use for later study phases. See http://en.wikipedia.org/wiki/Clinical_trial#Pre_clinical_studies (last viewed May 25, 2007). Furthermore, the present disclosure provides support for the fact that extrapolation of effective dosages are readily known in the art. Page 9, lines 18-21. Hence, it is clear that those of skill in the art would be able to practice the present claims based on the provided disclosure. For further references, see also the following: Prueksaritanont T., Subramanian R., Fang X., Ma B., Qiu Y., Lin JH., Pearson PG and Baillie TA. Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization. Drug Metab Dispos. 2002; May; 30(5):505-512; Schlenker RA. Skeletal 212 Pb retention following 224Ra injection: extrapolation of animal data to adult humans. Health Phys. 1988; 54(4): 383-396.

In any event, the Applicant submits further experimental data obtained by the inventors (Table 2). Table 2 provides additional studies involving human subjects and having 5 data points to evidence therapeutic change.

Thus, the Applicant respectfully requests that the above rejections be withdrawn.

Claim Rejections - 35 U.S.C. § 103(a)

The Examiner rejected claims 1-15 as being rendered obvious under 35 U.S.C. 103(a) by U.S. Patent No. 5,801,193 to Ojo-Amaize et al. ("Ojo-Amaize"), in view of Cybulsky et al., Endothelial expression of a Mononuclear Adhesion Molecule During Atherogenesis, Science, 1991, vol. 251, pp. 788-791 ("Cybulsky"), and further in view of Robbins Pathological Basis of Disease (5th ed., 1994, pp. 473-483)("Robbins").

More specifically, the Examiner alleges that Ojo-Amaize et al. teaches using hypoestoxide compounds as immunosuppressive agents (p. 8), Cybulsky et al. teaches that endothelial activation in the setting of atherosclerosis are present at sites of foam-cell aortic lesions in hypercholesteremic and/or hyperlipidemic rabbits (p. 9), and Robbins teaches that hyperlipidemia is an important factor in the development of atherosclerosis (p. 9). From these disclosures, the Examiner concludes that it would have been obvious to one of skill in the art to

use compounds shown to act as anti-inflammatories to treat hyperlipidemia as the references show that anti-inflammatory activities would aid in the alleviation of the inflammation associated with hyperlipidemia and subsequent progression of atherosclerotic lesions.

The Applicant respectfully traverses the above rejections for the following reasons.

There are many factors that may contribute to hyperlipidemia and atherscelerosis, known and still unknown, such it cannot be assumed that all compounds that can act as anti-inflammatories can also treat hyperlipidemia. The Applicant agrees that there is some link between inflammation and atherosclerosis, and that hyperlipidemia is a risk factor for atherosclerosis. However, an unequivocal connection between hyperlipidemia and inflammation cannot be made. Each drug must be evaluated on a case-by-case basis, as there are many different modes of action.

Furthermore, while hypoestoxide does have anti-inflammatory properties, its effect on hyperlipidemia has nothing to do with its anti-inflammatory action. Hence, this patent application is specifically directed to the treatment and prophylaxis of hypertriglyceridemia. Hypoestoxide's mechanism of action in anti-inflammation is linked to its ability to inhibit the activation of nuclear factor-κB. However, the ability of drugs to lower triglyceride levels is linked to their ability to agonise peroxisome proliferator-activated receptor (PPAR)α/γ. See e.g., Reifel-Miller, A. et al. *Mol. Endocrinol.* 2005 June; 19(6): 1593-1605; Guo, L. et al. *Eur J. Pharmacol.* 2006 Dec 3; 551(1-3):80-86. In fact, the inventors have found that hypoestoxide is a PPAR-γ agonist (unpublished data).

The connection drawn between inflammation and hyperlipidemias is not as simple or obvious as the Examiner contends. For example, dexamethasone (DEX) is a well-known corticosteroid that is used in many medical applications as an anti-inflammatory agent. When DEX was tested for its effect on blood lipids, it was found that it *increased*, not decreased, serum lipids in rats. See e.g., Bruder, E., et al. *Journal of Applied Physiology*, 98:981-990, 2005. Another study in rabbits showed that DEX treatment *caused* hyperlipidemia, but in spite of this, the treated animals had less atherosclerosis than the control animals. See e.g., Asai, K. et al.,

Atherosclerosis and Thrombosis, 13:892-899, 1993. Another well-known non-steroidal anti-inflammatory agent, indomethacin, was shown to have *no effect* on lowering blood lipids in monkeys, but was found to reduce the extent and severity of atherosclerosis in treated animals. See e.g., Dhawan, V., et al., *Canadian Journal of Cardiology*, 8:306-312, 1992.

Thus, the above are just a few examples of steroidal and non-steroidal anti-inflammatory agents that have no effect on (or even raise) blood lipid levels in experimental animal models, but yet, both gave some level of protection from atherosclerosis. Thus, the above literature references demonstrate that there is no dispositive showing that lowering blood lipids would provide a benefit in atherosclerosis.

Therefore, the present claims are not rendered obvious by the above-cited references for the reasons set forth above.

This response is being submitted within the three month deadline. In the case any fee is owed, please charge deposit account number 03-3975 (ref. 69081-306235).

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CONCLUSION

The Applicants believe that the foregoing Remarks place this application in a condition for allowance and earnestly request a prompt action on the merits. If, however, the Examiner believes that the present application is in a condition other than for allowance, the Applicants request that the Examiner telephone the undersigned attorney at the Los Angeles telephone number (213) 488-7100, if the Examiner believes that such a telephone conference will advance prosecution.

Respectfully submitted,

PILLSBURY WINTHROP SHAW PITTMAN LLP

Date: 6/26/2007

By: _____

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Enclosures:
(1) Biologic Markers in Urinary Toxicology (1995)
(2) Prueksaritanont T., Subramanian R., Fang X., Ma B., Qiu Y., Lin JH., Pearson PG and Baillie TA. Glucuronidation of statins in animals and humans: a novel mechanism of statin lactonization. *Drug Metab Dispos.* 2002; May; 30(5):505-512
(3) Table 2: Oral Consumption of *H. rosea* Dried Leaf Powder Lowers Triglyceride Levels in Human Subjects
(4) Reifel-Miller, A. et al. *Mol. Endocrinol.* 2005 June; 19(6): 1593-1605
(5) Guo, L. et al. *Eur J. Pharmacol.* 2006 Dec 3;551(1-3):80-86
(6) Bruder, E., et al. *Journal of Applied Physiology*, 98:981-990, 2005
(7) Asai, K. et al., *Atherosclerosis and Thrombosis*, 13:892-899, 1993
(8) Dhawan, V., et al., *Canadian Journal of Cardiology*, 8:306-312, 1992